NWX-Disease Control & Preventi (US)

Moderator: Dale Babcock
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11:00 am CT

Coordinator: Welcome and thank you for standing by. All participants will be (unintelligible) to listen-only until the question and answer portion of today's conference. To ask a question please press star 1. Today's conference is being recorded. If you have any objections, please disconnect at this time. I would now like to turn the conference over to Dr. (Raymond Strickus). Sir, you may begin.

Dr. (Raymond Strikas): Thank you very much and welcome to Current Issues Immunizations Net Conferences presented by the Immunizations Services Division, the National Center for Immunization Respiratory Diseases at the Centers for Disease Control and Prevention, CDC in Atlanta, Georgia. To participate in today's program you should have a telephone connection and a separate Internet connection to hear the information and see the information presented.

The learning objectives for today's sessions are to describe an emerging immunization issue, to list a recent immunization recommendation or more than one made by the advisory committee and immunization practices, be able to locate resources relevant to current immunization practice and to obtain, assess and apply patient information to determine the need for immunization.

Today's agenda has one topic; we will cover the epidemiology prevention of vaccine preventable diseases webinar series from the pink book on general recommendations part two and the second topic, vaccine safety to be presented by Dr. (Andrew Kroger) to complete the session he began last week.

Now please make a note, if you have technical difficulty during today's program you can dial star 0 to access the operator. To ask a question later during our question and answer session please dial star 1. Continuing education, or CE credits, is available only through the CDC ATSDR training and continuing education online system, which his at the website there - www.2a.cdc.gov/tceonline/. Continuing education credits for this program today expires on August 24, 2015.

When obtaining CE you'll be required to provide a verification code that I'll give you later. Please watch and listen for that code during this program. The verification codes will not be given out side of this presentation. CDC, our planners and our presenters wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. Planners (unintelligible) the content of this program insure there is no bias.

Presentations, including today's, will not include any discussion of the unlabeled use of a product or product under investigation (unintelligible) with the exception of Dr. (Kroger)'s discussion of avoiding conception for one month following administration of a live vaccine. CDC does not accept any commercial support. Let me now turn the microphone over to Dr. (Kroger).

Dr. (Andrew Kroger): Thank you Dr. (Strikas). It gives me pleasure to present to you today from Atlanta. Today's presentation covers two topics. The first is general recommendations on immunization part two. The second is vaccination safety.

The flow of my presentation will correspond to the later part of the second chapter of the 13th edition of Epidemiology and Prevention of Vaccine Preventable Diseases or PINK book, which begins on page 28.

Part of that discussion I'll discuss is the topic of invalid vaccine contraindications. This is a topic that's discussed in both the general recommendations and the vaccine safety chapter. Then I will discuss the vaccine safety chapter, which is chapter 4 of the PINK book. The slides that I'm using are similar to the graphics that you'll be seeing in the margins of the PINK book and I will be posting these slides in the near future.

To recap a bit from last week's presentation, the term or concept "General Recommendations on Immunization" refers to those recommendations that apply to all vaccines. CDC guidance often comes in the form of a single vaccine-specific recommendation, but in practice you have to deal with as many as 15 vaccines given routinely to patients depending on age. There's a canon of guidance to address situations commonly encountered in vaccine practice, essentially applicable to all vaccines. CDC publishes this guidance in a Morbidity and Mortality Weekly Report in the Recommendation and Reports series.

Since the original publication of the general recommendations in 1976 there have been eight revisions, the last in 2011 pictured here. This document is 62 pages long with 239 citations and we anticipate posting another revision to this guidance in about a year, perhaps sooner. CDC generates this guidance based on the deliberations of the Advisory Committee on Immunization Practices or ACIP - a non-governmental advisory group of 15 members that meets three times a year in Atlanta and makes recommendations to the CDC. So this MMWR is considered not only CDC guidance, but ACIP recommendations.

Last week I concluded my comments with a discussion of contraindications and precautions. Contraindications are conditions in a vaccine recipient that should cause you to withhold a dose of vaccine. Precautions are conditions in a vaccine recipient that may cause you to withhold the dose of vaccine and these conditions may be permanent or temporary. Today I'm going to begin with a discussion of screening, which is the best way to identify contraindications and precautions.

Screening questions are specific questions used to identify contraindications and precautions to vaccinations. Some conditions are temporary so they not only come and go, but they can come again. So it's important that you screen at every immunization encounter, not just before the first does of a series. A standardized form can be used so that screening can be done efficiently and effectively.

As I go through this set of questions, it's going to provide an important recap to the most important contraindications and precautions that I described in detail last week. The following questions are written from the perspective of a pediatric patient, but these questions can be adjusted for the adult patient population as well.

The first basic question is, "is the child sick today?" This identifies acute, severe or moderate illness, which is a precaution for all vaccines and is a common question that is part of every health encounter.

The next one, "does the child have an allergy to any medications, food or any vaccine?" So with this question the most common allergens can be identified by the patient or parent and then can be cross checked against lists of vaccine components. This is an acceptable way to proceed because the types of allergy

we are looking for are severe anaphylactic allergic reactions. That is the specific contraindication. These will be recognizable to parents and they're extremely rare as well.

"Has the child had a serious reaction to a vaccine in the past?" So this also identifies potential anaphylactic allergy. The question may also pick up past causes of other conditions like encephalopathy following pertussis vaccine. Remember, that's a contraindication if not attributed to something else and occurring within seven days of a pertussis-containing vaccine. Or other conditions: past cases of fever or seizure; limp, pale episodes; or uncontrollable crying for three hours straight following pertussis vaccine. These are precautions for further doses of Pertussis containing vaccine in young childhood.

Some more questions – "has the child had a seizure, brain or nerve problem?" This will also identify encephalopathy and seizures, as mentioned before, relevant to pertussis-containing vaccines.

"Has the child had a health problem with asthma, lung disease, heart disease, kidney disease, metabolic disease, such as diabetes or a blood disorder?"Children with these conditions probably should not receive the live attenuated influenza vaccine, LAIV. This is a precaution and if both live and non-live influenza vaccine are available they should receive an activated influenza vaccine.

You should ask 'does the child have cancer, leukemia, AIDS or any other immune system problem?'. This will identify a history of immunosuppression or current immunosuppression, which is a general contraindication to live vaccines.

Likewise, "has the child taken Cortisone, prednisone, steroids, or anti-cancer medications or had x-ray treatments in the past three months?" A history of immunosuppressive therapy, for example, with the medication treatments listed here, is considered immunosuppression and so also is a contraindication to live vaccines. Note, I've listed a three month washout period, but for some treatments, like low-dose steroids, low dose Methotrexate, one month intervals may be appropriate. We're being a bit conservative with these screening questions and it makes sense to do that.

"Has the child received a transfusion of blood or blood products or been given a medicine called immune or gamma globulin in the past year?" This question is relevant from both a safety perspective to uncover potential chronic diseases or immunosuppression that you want to know about, but also it's important because there are intervals you need to wait for some of these treatments to MMR and varicella vaccine. And as mentioned last week, that wait can be as long as 11 months and that's an effectiveness concern for MMR and varicella vaccine.

The next question, "is the child or teen pregnant or is there a chance she could become pregnant during the next month?" Pregnancy is a general contraindication to live vaccines and the period after live vaccines for which we recommend avoiding conception is one month.

Ask if the child has received vaccinations in the past four weeks. This identifies a recent history of live vaccines, which requires a four week interval for non-simultaneous vaccination. Note also that there are also some important intervals between some inactivated vaccines - it's a four week interval required between PCV-13 and (Menactra) brand Meningococcal vaccine - or MCV4D and also there is an eight week interval you have to be

aware of between two brands of inactivated pneumococcal vaccines, PCV13 and PPSV23.

These screening questions are available as a formatted tool courtesy of the immunization action coalition and is available on their website, which I will provide on a later slide. There is an adult immunization screening form as well as a child/teen immunization screening form.

Now I would like to discuss invalid contraindications. These are conditions that are often misunderstood by providers as a reason to withhold a dose of vaccine. Since these are not true contraindications or precautions, if a dose is withheld it reflects a missed opportunity. I have mentioned that moderate or severe acute illness is a precaution to vaccination, however, many providers misinterpret that to mean that vaccines should only be given to completely healthy persons at well visits. This is not true.

So mild illness is one of these misperceptions. Studies have looked at vaccination of persons with low-grade fever, upper respiratory infection, otitis media and mild diarrhea and in all of these cases there were no safety concerns when vaccines were administered. So that's why we described mild illness as an example of an invalid contraindication. You can vaccinate someone with these specific conditions so as not to miss an opportunity.

Another circumstance that often is confused by providers is the vaccination of household contacts of pregnant women. Household contacts should receive MMR and Varicella vaccines. They should receive either non-live influenza vaccine, i.e. various types of inactivated influenza vaccine products, or live attenuated influenza vaccine (LAIV). And zoster vaccine and rotavirus vaccines are given at the extremes of life - so a patient in these age ranges are perhaps less likely to be in contact with a pregnant women if there are

circumstances that a household contact is eligible for zoster or rotavirus vaccine, the vaccine should also be administered.

So basically the benefit of protecting a pregnant woman from transmission of disease from their contact, and all of the complications of the vaccine preventable diseases, which can be worse in pregnancy, we make the recommendation that to vaccinate a household contact using a live vaccine microbe outweighs thet risk of the live vaccine microbe because of the importance of protecting the mom, so they should be vaccinated. The risk of live vaccine virus transmission is close to zero, with the exception of varicella vaccine. With varicella vaccine there's a possibility of transmission if the vaccinated person has a rash. Even though varicella disease can affect a fetus, varicella vaccine has not been show to injure a fetus and in most circumstances a mom is already immune from varicella anyway and will not have the complications of varicella.

Another invalid contraindication is pre-term birth, which means less than 37 weeks gestational age. Generally, infants and children should be vaccinated according to chronologic age with no need to account for the gestational age. And full doses of vaccine are recommended as well. Birth weight and size are not factors and there is one exception to this - Hepatitis B vaccine. Now this vaccine is routinely recommended at birth. If an infant is pre-term and has a mother who is Hepatitis B surface antigen negative, and that is documented, then a dose of Hepatitis B vaccine can be delayed until discharged from the hospital or chronologic age one month. This really is an effectiveness issue. We want to have the maximum effectiveness of the Hepatitis B vaccine - maximizing the response.

However, note that if mom's Hepatitis B status is unknown or positive this exception goes out the window and it becomes more important from a safety

perspective since Hepatitis B vaccine is effective in preventing neonatal transmission of the Hepatitis B virus. The exception goes out the window and vaccination must occur at birth, which is, again, the recommended time for vaccination to obtain protection from the potential Hepatitis B disease exposure.

So I'm going now to transition to a discussion of vaccine safety. If you are following along in the Pink Book you should jump ahead one chapter to chapter 4. I'm going to divide my comments into some general principles about why vaccine safety is an important topic, how CDC monitors vaccine safety and the role that providers can play in assuring vaccine safety. As far as the provider's role, I've already talked about screening, but I will go further and I'll elaborate on some principles of risk-benefit communication.

Let's first begin with a discussion of why vaccine safety is such an important topic. So this table lists the average annual morbidity in the 20th century for a variety of vaccine preventable diseases that was documented in a JAMA article in 2007. That's in the second column - note in the third column the number of cases in 2014 for the same diseases. In the right hand column is displayed the percent decrease in disease morbidity. A quick disclaimer - I'll make the point that the table in your Pink Book chapter has slightly different numbers. The current year in that chapter is 2006 instead of 2014 and also the comparison morbidity data from the 20th century is not an average over the entire period of time during the 20th century. It reflects data collected from a point in time prior to the 2007 data. So in a sense the table you're looking at right now on the screen is more up-to-date.

The important point is, for all of this, is that in the right hand column this data is a success story for vaccines, first of all. You can see the reduction in disease and also look at the bottom row of this table, which lists the average number

of adverse events reported to the vaccine adverse event reporting system. It's around 30,000 a year and then look at the column for 2014 and notice that this 30,000 number - move up one cell - is close to the total number of cases seen for all vaccine-preventable disease. Providers and parents are almost more likely to see an adverse event, and these 30,000 are just the reported events. So providers and parents are almost more likely to see an outcome like this following a dose of vaccine and perhaps reported as an adverse event than they are likely to see a vaccine-preventable disease. So adverse events are very visible.

Because vaccines are universally recommended - or mandated - they are given to large numbers of people. We anticipate a lot of reporting of adverse events and we also realize that any safety problems that might exist with vaccines have the potential to impact a large number of people. This is why we have ongoing safety monitoring and this is needed for the development of sound policies and recommendations.

Public health constantly weighs the burden that disease places upon a population, which is why we have vaccine as a public health initiative and we weigh that disease burden against any new vaccine risks that might be identified with such large numbers of people receiving the vaccine. Certain vaccines have in fact been discontinued - like small pox vaccine and polio vaccine in some places when it was determined that risks from the vaccine outweighed the benefit. When the disease disappeared we stopped using the vaccine.

Also, as I showed on the first safety slide with the table - as disease risk decreases the concern about vaccine risk is going to increase. Many providers and parents have never seen a case of *Haemophilus influenzae* type b invasive disease or have never seen Measles. So public confidence in vaccine safety is

critical. When I use the word public I'm speaking broadly to include patients and providers. We expect a higher standard of safety from vaccines compared to other medications. Vaccines are administered to people who are healthy as opposed to ill for medications.

So we're less tolerant of risk from vaccines and there is a need to search for those rare reactions that might exist. And that search goes on not only before the vaccines are licensed, but even after the vaccines are licensed. And, again, to repeat the fact that vaccines are universally recommended and mandated is another reason why there's going to be less tolerance for vaccine risk on a population basis. Vaccines are recommended for all of us and so the vaccine safety issue affects all of us.

From a communications perspective it's important to state upfront that we're not defining safe as no harm from the vaccine. Because no vaccine is 100% safe. It's also misleading to say that vaccines will make someone 100% safe from the disease - because no vaccine is 100% effective in preventing disease. Years and years of research go into the research, development and production of vaccines to create a product that has what we hope is close to a zero risk of any type of severe outcome from vaccines and also we'll come close to 100% in preventing severe complications from the disease and the vaccine will prevent the disease. So just keep in mind nothing is 100%.

Parents should be reminded that until a disease is eradicated there's a risk of the disease occurring and a risk of disease-based complications occurring. And so to avoid a dose of vaccine and to do nothing also involves taking a risk.

Like other pharmaceutical products vaccines undergo extensive laboratory studies to understand the mechanism of action and this has safety and efficacy

implications. Vaccines are then studied in animals and attempts at safety and efficacy comparisons are made to humans. We always err on the side of safety for humans when it comes to the volume of the dose which is given to animals that are smaller - so we adjust.

Finally, extensive phase studies are carried out in humans. And the phased trials are divided into three stages 1, 2 and 3. Phase 1, human clinical trials usually involve anywhere from 20 to 100 volunteers. They focus on the serious side effects. Phase 2 trials enroll hundreds of volunteers. They may last a few months to a few years. Safety is an important focus with the phase 2 trials, but tests are also looking at how the human immune system responds to the vaccine. These trials determine the most effective use of the vaccine, the best dose for effectiveness and safety and the correct number of doses.

Phase 3 trials involve a few hundred to several thousand volunteers. They may last several years. Phase 3 trials include a control group. They receive either a placebo or another already licensed vaccine. Allowing researchers to compare one vaccine to another or to a placebo for adverse health effects. And, of course, also to calculate the efficacy.

Most phase 3 trials can identify common reactions. They usually include 2000 to 5000 participants. The largest phase 3 trial in the last several years was the Rotavirus Efficacy and Safety Trial - the REST trial, which included 70,000 infants. The trial needed to be this large in order to asses for a relatively uncommon possible adverse event that was associated with a previous rotavirus vaccine, intussusception. . And so that’s why this trial was that big - to detect that, and so it had that many people and the trial observed that intussusception was no more common in vaccine recipients than among placebo recipients.

Once a vaccine is shown to be safe and effective in phase 3 trials the manufacturer applies for a license from the Food and Drug Administration, or FDA. During the application the FDA reviews everything - clinical trial results, product labeling, the plant itself, the manufacturing protocols. So while rates of common vaccine reactions such as injection-site reactions and fever can be estimated before licensure there are comparatively small numbers of patients in these trials - 2000 to 5000 usually, which limits detection of rare side effects, and ones that could affect many months after the vaccine is given. There are side effects that may occur in certain sub-populations. So it's important to monitor reports of adverse events once the vaccine has already been licensed and released for public use. So this is post licensure surveillance.

Post-licensure surveillance identifies rare reactions. Post licensure safety surveillance can also monitor increases in reactions that are known already and more importantly can identify certain risk factors that may contribute to the adverse reactions. Post licensure safety surveillance also can collect programmatic information like lot numbers from the vaccine. So can identify if increases in adverse reaction rates are associated with specific lots. And then last but not least our post licensure surveillance can identify signals. These are adverse events that are more numerous than would be expected, usually looking across all vaccines. These may be events no one has considered previously. So this is one way that adverse reactions can be discovered.

The Vaccine Adverse Event Reporting System - or VAERS - was created in 1990 and is jointly administered by the CDC and the FDA. It is a national passive reporting system to collect all reports of clinically significant adverse events reported by manufacturers, health care workers and the general public. VAERS receives about 30,000 reports per year and that's 130,000 reports to

date. That seems like a large number, but it is relatively small compared to the approximately 100 million doses of childhood vaccines that have been distributed during the past decade as well as millions of additional doses given to adults.

I did discuss VAERS in last week's presentation. This is a tool that seeks to capture all clinically significant medical events occurring post-vaccination. Even if the reporter is not certain that the incident is vaccine-related. Despite some limitations VAERS has been able to fulfill its primary purpose of detecting new and or rare vaccine adverse events, increases in rates of known side effects, and patient risk factors for particular types of adverse events. For example, VAERS tracked and raised the concern about intussusception after the Rotashield rotavirus vaccine in the 1990s and also tracked anaphylactic reactions to MMR vaccine caused by gelatin allergy.

VAERS cannot establish causality. Additional studies are always required to confirm signals detected by VAERS because not all events are causally related to the vaccine. Simply because a health problem occurred after vaccination does not mean that the vaccine caused the health problem. The reportable events table in your pink book, appendix D2, lists what's reportable by law to the Vaccine Adverse Event Reporting System. It includes conditions listed in the manufacturer's package insert, but of course health care providers are encouraged to report any clinical significant or unexpected events. Even if you're not sure the vaccine caused the event and whether or not it is listed on that table. Manufacturers are also required by regulation to report to the VAERS program all adverse events made known to them for any vaccine.

And just another reminder that because something is reported to VAERS or if we suggest you report something to VAERS it doesn't mean that this event was caused by the vaccine. The Latin dictum, post hoc ergo propter hoc,

translated “after this therefore because of this”, is known as the ecologic fallacy. This is a fallacy because temporal association does not prove causation. Causation has to be determined after two occurrences have been studied statistically and even at that point when we have a statistical association we call that a correlation, not causation.

So just think about it for a minute how coincidences happen. You know, here is a crude example - someone can get in a car accident on the way home from the vaccination clinic. That does not mean that the vaccine dose caused that accident. There are coincidences that occur. If there is determined to be a correlation between a vaccine and an outcome there are additional ways that the interaction can be explored. The duration of time between the exposure and the event, whether the event has ever been seen before, whether it can be shown to occur again. Some events can be demonstrated in the laboratory if there is a biologic mechanism. Laboratory studies can be done to look at a dose response as well. So all of those things can be performed to determine whether a correlation is causation.

But first, correlation has to be determined. So let me explore some of the ways that adverse events can be evaluated. First of all, to truly assess correlation of an adverse event with a vaccine you need four pieces of information. You need to know the number of people who received the vaccine that had the outcome or disease as listed on this table that have the outcome of interest.

On this table that would be a number that would belong in cell A. You also need to know how many people that received the vaccine did not develop the event. On this table that’s marked by cell B. You also need to know the background rate of that same event of interest. You do this by identifying an unvaccinated group and determining the number of people in that group that

did and did not have the event of interest. This would correspond to cells C and D respectively in the table.

These four pieces of data will then allow you to calculate the rate of the event in the vaccinated group. That would be A divided by A plus B. And the background rate of the event, which would be the event in the unvaccinated population - or C divided by C plus D. If the rate in the vaccinated group is higher than the rate in the unvaccinated group, and other factors have been controlled for: e.g. age, underlying conditions, we could then say that the vaccine is correlated to the outcome and further study can be undertaken to determine if causation exists.

I've talked about VAERS. The VAERS system provide only one of these important pieces of information, cell A. Number of events that occur in a population of vaccinated persons. It's a passive reporting system. You're only going to capture people that receive vaccine and report the event. So that's why VAERS alone cannot be used to assess whether or not a vaccine is correlated to an event. So with VAERS reports we sometimes receive signals and additional studies are needed, which would need numbers in all four of these cells to determine if there is true correlation.

Here's an example of a study that looks at this mathematically. So these are actual data published in the 2002 New England Journal of Medicine that looked at autism spectrum disorder - or ASD among MMR-vaccinated and unvaccinated children in Denmark between 1991 through 1998. The vaccine row shows that of those who received the vaccine 345 people had a ASD and 440,310 people did not have ASD.

So notice how important cell B is in this figure. It looks like 345 is a large number of cases, but not when you realize how many people were vaccinated

without experiencing this outcome. Now look at the bottom row of the table, of the persons who did not receive vaccine 77 had ASD an 96,571 did not. So the number - the total number of people in that bottom row - if you do a quick eyeball of the numbers - the bottom row is much smaller than the top row, isn't it? So Denmark is a country that has good coverage with MMR vaccine. Also the number 345, again, doesn't look large stacked up over the 400,000 people who received the vaccine and did not have ASD.

So by calculating the fractions A over A plus B and C over C plus D (and these fractions have been simplified to have a common denominator of 10,000)you can compare the overall rate of ASD and those who received the vaccine and those who did not receive the vaccine. Ironically the rate of ASD is higher in those that did not receive the vaccine. The reality is that this difference is not significant and so the numbers are the same. And what this means is that there is not a correlation between autism spectrum disorder and MMR vaccination in this study.

So that's what's needed - trials like this and so this brings me to other post licensure types of evaluations. They include phase 4 studies typically conducted by manufacturers in partnership with others, and can include 10s of thousands of volunteers and they can address questions of long-term effectiveness and safety. Or examine unanswered questions identified in phase 3 studies to obtain data from even more individuals. Other post licensure tools that are out there include the vaccine safety data link - this is an example of a large linked database or the Clinical Immunization Safety Assessment project. For these last two the CDC is an active partner in these projects and I'm going to discuss these further.

So the Vaccine Safety Datalink is a large linked database or LLDB, which means that it connects computerized pharmacy prescriptions and

immunization records with computerized medical records. The LLDBs are derived from defined populations such as members of managed care organizations, HMOs, single provider healthcare systems and Medicaid programs. The data are generated in the routine administratione of these programs and so these databases do not require the completion of a vaccine adverse event reporting form. So it reduces problems of underreporting or recall bias. These are populations that are under active surveillance rather than passive surveillance and so we're collecting information from people that receive vaccines and do not receive vaccines. So it really allows for the establishment of correlations and causal relationships and timely analysis as well.

So the VSD specifically links immunization and medical records from nine HMOs totally more than 3% of the US population and these HMOs in partnership with the CDC plan and execute immunization safety studies. They do investigate hypothesis from the medical literature, VAERS reports, as well as changes in the immunization schedule or the introduction of new vaccines. The Clinical Immunization Safety Assessment project was established in 2001 as a network of seven centers with vaccine safety experience in partnership with the CDC. The network is designed to improve the understanding of vaccine safety issues at the individual level.

This network of coordinated facilities investigates and manages vaccine side effects on an individual basis for the purposes of providing patient care. It also systematically collects and evaluates data on these experiences in order to gain a better understanding of how such events might occur and to develop protocols or guidelines for healthcare providers to help them manage similar situations. CISA also conducts studies to identify risk factors and has contributed to the development of ACIP recommendations. So that's a summary of the systems in place to assure vaccine safety and to monitor it for

adverse events. In spite of these efforts rare adverse events occur. What happens then?

Well we have the Vaccine Injury Compensation Program. A bit of history - during the 1970s lawsuits concerning vaccine adverse events were filed resulting in legal decisions and damages awarded despite lack of scientific evidence to support the claims. As a result of this liability vaccine prices soared and several manufacturers stopped vaccine production. Vaccine shortages resulted and there was concern about the return of epidemic disease. This situation led to the National Childhood Vaccine Injury act of 1986, which in turn established the vaccine injury compensation program. You can see a website of the vaccine compensation program here.

This was intended to compensate individuals who experienced certain health events on a no-fault basis, meaning that they aren't required to prove negligence to receive compensation. The program covers all routinely recommended childhood vaccines and the settlements are based on a vaccine injury table, which is located in your pink book appendix, pages D5 and D6. The table lists and explains injuries and conditions that are presumed to be caused by the vaccines. It also lists the time period in which the first symptom of these injuries and conditions must occur after receiving the vaccine. So now we've talked about processes to insure vaccine safety and compensation for rare cases of injury. Now I'd like to talk about the provider's role in assuring vaccine safety.

So given all of the projects that I've mentioned previously, the provider has additional roles to assure vaccine safety. It includes storing and handling vaccines correctly, scheduling the vaccines at the appropriate times, screening for contraindications and precautions, managing adverse reactions after

vaccination, reporting adverse events to VAERS and communicating effectively the benefits and risks of vaccinating.

So as far as these bullet points - the storage and handling and the administration of vaccine will be discussed in future webinars. I've already discussed timing and spacing and screening for contraindications and precautions. For management of adverse reactions, I'll mention that as a minimum provider should have epinephrine and equipment to maintain an airway. This is to manage anaphylaxis which is the most important of the adverse reactions to be aware of. Many of you will not see it because it occurs at a rate of one case for every 1.5 million doses of vaccine. However, you need to be prepared. Your office should have an emergency plan and providers should be certified and cardiopulmonary resuscitation. I've already discussed reporting to VAERS and so now I want to focus on this last item on this list - benefit and risk communications.

So before each vaccination providers need to inform parents, guardians, legal representatives of the benefits and risks of vaccine in a language they understand. Opportunities for questions need to be provided before each vaccination. The National Childhood Injury Act requires the use of Vaccine Information Statements, or VISs, which must be provided before each dose of vaccine. If the vaccine in question is administered to a recommended age group encompassing zero through 18 years. This is a requirement for both public and private sector providers.

The VISs are available in English on the CDC website, but they're also available in multiple other languages. To obtain the VISs in other languages please visit the Immunization Action Coalition site at www.immunize.org. So that's how to obtain the VIS. Now it would be great if the legal VIS document addressed every possible question a patient or parent may have. As it is that's

not the case and you as a provider still need to anticipate the types of question and concerns of parents that will be coming.

You need to realize that parents are being flooded with information on the internet and other media as well. And so celebrities claiming to be health advocates, are giving health information based on personal experience and will be weighing in. This is an image of Jennifer McCarthy who was published in People when she claimed that her son's condition was due to a vaccine. She did not use science to back her up on this, but her words carried weight because she is a celebrity.

Public health also looks to other celebrities who advocate for vaccination. Their efforts are helpful. This slide shows Amanda Peet, Jennifer Lopez and Campbell Brown. They've all discussed the importance of vaccination - primarily in the context of Pertussis and Measles outbreaks, which often result in part from vaccine hesitancy. These efforts are very very helpful, but I would like to now move on to You as the provider because your recommendation has even more power.

Studies show that just communicating with parents and as a provider if you make a recommendation parents are more likely to have their children vaccinated. When parents express a concern it's important that you ask questions so that you fully understand what the concerns are. Acknowledge that the parent has the concern - use empathy. And then provide advice. Starting your interaction at the prenatal visit is important as continuity of care is a way to establish trust. You need to be aware of the resources that are available that parents will be bringing. I've showed some slides about celebrities and you have to know what the concerns are, but you have to know reliable resources with the science to give to the parents.

Find common ground with the most resistant parents. Accept that you may not get a parent to accept all vaccines. You should not kick parents out of your practice because if they don't have a healthcare provider it's going to be even harder for them to receive the vaccines and care they need, but you have to document vaccine refusal. That's very important, but try not to get defensive in your interactions.

So I'm now going to talk about some of the science around a common concern - autism. I've already discussed a study from Denmark and the epidemiology that really supports the facts that there's no association between MMR vaccine and autism. There are other studies that have been conducted to successfully counter claims that MMR or other issue like thepreservative thimerosal somehow are associated with autism, but this partial list of studies that have looked at both of the MMR and the thimerosal issues debunk any correlation. They show no correlation exists.

Once enough of these studies became published the tide did start to turn in favor of science. And then, of course, later advocacy organizations like Autism Speaks reached the same conclusion and communicated that autism is not associated with vaccination. This is a quote from Dr. Geri Dawson who stated in 2009, "Given what the scientific literature tells us today there is no evidence that Thiomersal or the MMR vaccine causes autism. Evidence does not support the theory that vaccines are causing an autism epidemic."

So other organizations as well also have helped tremendously to communicate that this association does not exist and that we have a shared goal in trying to find the true cause of autism and it's time to stop expending our efforts on theories like MMR and Thiomersal.

In 2011 the Health Resources and Services Administration asked the institute of medicine or IOM, which is part of the National Academy of Sciences, to review a list of adverse events associated with eight vaccines. The vaccines were varicella-zoster, influenza, hepatitis B, HPV, MMR, hepatitis A, the Mmeningococcal vaccine, and those that contained Tetanus. To look at the scientific evidence about various events including autism and vaccines the IOM committee appointed to this task was not asked to assess the benefits or effectiveness of vaccines, but just to focus on specific adverse events and then using Epidemiology and the other mechanisms for establishing causation that I described earlier.

The committee developed 150 causality conclusions and assigned each relationship between a vaccine and an adverse health problem to one of four categories of causation. The committee found that evidence convincingly supports a causal relationship between some vaccines and some adverse events such as MMR, varicella-zoster, influenza, hepatitis B, meningococcal, tetanus-containing vaccines and Anaphylaxis.

So that's an example of causation that IOM gave support to. However, they rejected five adverse event vaccine relationships including MMR and Autism as well as the trivalent influenza vaccine , or TIV, and asthma. For the majority of cases (it was 135 vaccine adverse event pairs), the evidence was inadequate to accept or reject a causal relationship. However, overall, the IOM did conclude that few health problems are caused by - or clearly associated with vaccines.

I do want to talk of another common concern of parents and some methods of communication that are important. This is the issue of delayed or alternate schedule. Parents, you know, have a tendency to want to use these schedules because we do recommend a lot of vaccines. They're looking for facts and

statistics and websites that they can trust. It's important when you have these discussions that are there are studies that support simultaneous vaccination. There also are textbooks that explain how the immune system is physiologically capable of responding to hundreds of thousands of antigens throughout life, but the key is to share these sources of that information. So share the good websites that can be trusted that have the information and talk to parents, but don't talk down to parents: use unbiased, non-coercive language and be non-judgmental as well.

For my final slide I do want to talk about the IOM again. So the Department of Health and Human Services - National Vaccine Program Office requested from the IOM to convene a committee on the assessment of studies of health outcomes related to the Recommended Childhood Immunization schedule and to conduct an independent evaluation of the studies of the safety of the Childhood Immunization Schedule. They issued the report on January 16, 2013. In it the committee expressed support the for the childhood immunization schedule as a safe and effective tool to protect against vaccine preventable diseases.

The committee recommended using existing healthcare data to continue the study of safety of vaccines. The committee also reconfirmed a finding of the National Vaccine Advisory Committee that conducting a study, which required some children to receive fewer vaccines in their recommended schedule would be needed for a randomized control trial, would be unethical to do. It would withhold important vaccines and put children at risk of vaccine preventable disease. So the current recommended immunization schedule, as published by CDC, the ACIP and the professional academies does have flexibility and is the best way to optimize protection from vaccine preventable disease at times when children and adults are at highest risk and can respond to the vaccines.

So on that concluding point I'm going to move on to a poll question covering the entire day's presentation. Which of the following is a true statement: A - pregnancy is generally contraindication to live vaccines; B - if a patient has a mild illness a vaccine should be withheld until a later date; C - moderate or severe illness is a contraindication to live vaccines; or D - where a contraindication is present providers should weigh the risks and benefits of administering a vaccine?

So why don't you take 10 seconds and input your answer and then we'll go over the question. Okay, time is up. And a majority of you – barely, 56% of you chose A – "pregnancy is generally a contraindication to live vaccines." And that is the correct answer. Let me go through the other options. So for B - no one said B. B is incorrect because mild illness is neither a contraindication nor a precaution to vaccination and vaccines may be given to someone with mild illness, so as not to miss an opportunity to vaccinate. C - moderate or severe illness is a precaution, not a contraindication as listed in the question to live and inactivated vaccines. There may be circumstances where it still may be advisable to give a dose of vaccine. It requires a risk-benefit analysis. 27% of you actually selected D. I was kind of tricky here, where a contraindication is present providers should weigh the risks and benefits of administering a vaccine. Generally this is more a definition of an action step for a precaution, not a contraindication. With a contraindication our general recommendation is to withhold that vaccine. We're more general about it. There are very specific examples where allergists may be able to conduct studies that allow administering a dose of vaccine, however generally you should withhold a dose of vaccine. That's the reason that D is wrong. So the majority of you got the right answer. So good job.

And I will now turn the mic over to Dr. (Strikas).

Dr. (Raymond Strikas): Well thank you very much Dr. (Kroger). We're going to move the questions and answers, and I'm going to give you some information about that, as well as I want to go through two slides besides this one on the continuing education credits that you need to have, before we do questions and answers. As you're getting ready to answer - ask your question, please dial star 1 to get in the queue for operator.

Now we will have a recast of this program available on the internet on our website at www.cdc.gov/vaccines/ed/ciinc next week. That is the week of July 27. The slides will be there, as will the audio portion and other resource information.

Now for continuing education information this is important. Again the website you've seen before, but its worth noting - www.2A.CDC.GOV/TCEonline. The course number for this program is date specific and the letter is E as in Edward, C as in cat, 2064-072215- that's today's date - 072215. You need that for completing CE requirements. The verification code is EPI-safety for today's program only.

So you need that verification code EPI-safety and the CE credit for this program expires in approximately one month - August 24, 2015. I'll repeat this information at the end of the question and answer period, but for those that may have to leave before then here is the verification code and the course number that you need for CE. Let me now turn it over to the operator to please let us have our participants ask the questions they wish to ask. Operator?

Coordinator: Thank you. Our first question comes from (XXXXXXX), your line is open.

(XXXXXXXX): Yes, I just - I have a question about Hepatitis B. Hepatitis B I know is given as soon as the children is born, but what I find that I wanted to know if CDC would recommend a second round of Hepatitis B vaccines when the kids are like 15-16 because I find a lot of the kids (unintelligible) no immunity around their 15 and 16. I even have the problem with my children when they're 15 and 16 and even 17, my daughter is ready to go off to college and we have to re-immunize her with Hepatitis B because she has no immunity and at this age where the children are most vulnerable. So I would recommend if CDC can do a second round of Hepatitis B or do some more studies in that area.

Dr. (Andrew Kroger): Thank you for that - that's a great question and actually the - we don't recommend a second round of Hepatitis B vaccine in that circumstance. And the reason is is that just because - if someone has the Hepatitis B series at a young age in infancy at age 15 and 16 even though someone has a serology test performed that is negative, it doesn't mean that that person doesn't have immunity to Hepatitis B. There are other components of the immune system that are not detectable on routine laboratory tests that provide the immune response and so someone may be protected and still have a negative test. This is an issue over time if the test is done that long after - 15 or 16 years after the vaccine was given in infancy. So we actually expect negative results on that and it doesn't mean that the person is not protect.

And we know that because when we give one single dose, which normally, you know, a person's first dose doesn't generate a very strong immune response, but when we give a fourth dose it has an extremely high antibody response. SO what's happening is there is a response - the person respond to the vaccine and their immune system generate the immune response that is protective and that is sufficient for Hepatitis B because the Hepatitis B virus has a very long incubation period and so the immune system has time to rev up to provide protection.

And so routinely there's not thought to be a need for booster doses after the first series of vaccine. We do have slightly different recommendations for healthcare providers that are going to be exposed to Hepatitis B virus as part of their occupation. So anyone with exposure risk we have a slightly lower threshold for giving additional doses of vaccine if a test is negative. And there's more information on that in CDC's MMWR from December 2013, but I guess we can take the next question.

(XXXXXX): Thank you.

Coordinator: Our next question comes from (XXXXXX). Your line is open.

(XXXXXXX): Thank you - my question was in so far as like contraindications for the live virus vaccines. Say there was a patient that had received in the past three months like three short courses of Prednisone for an asthma exacerbation. Would then you need to wait further to give the live virus vaccine?

Dr. (Andrew Kroger): That's a great question. We discussed some of this during the last week's presentation on the definition of immunosuppression and Corticosteroids and we have defined certain parameters for use of Corticosteroids and they do involve daily dosing of 20 milligrams a day or 2 milligrams per kilogram per day for a period of two weeks. And we kind of stick to our guns when it comes to using that as the definition of immunosuppression, so much so that if we talk about alternate day doses, we talk about tapered regimes, we say that those are NOT immunosuppressive. So I think it's important to also note that the ultimate decision on whether a patient is immunosuppressed does fall with the provider that prescribing the medications. When it comes to regimes of Corticosteroids that may have time intervals, you know, between their use we typically do not label that as an immunosuppressive dose. So, you know, the

short answer to the question therefore is no, but again you always want to be flexible and make sure that - if you're making that decision you're the provider that's the one giving that medicine.

(XXXXX): Okay. Okay, thank you.

Dr. (Andrew Kroger): Yes, you're welcome.

Coordinator: Our next question comes from (XXXXXX). Your line is open.

(XXXXXXX): Yes, can you hear me?

Dr. (Andrew Kroger): Yes, we can hear you.

(XXXXXXXX): Okay, great. I was wondering if you could please restate the reasoning for the minimum interval between pneumococcal - excuse me - pneumococcal 13 and Menactra and also may they be given simultaneously if possible?

Dr. (Andrew Kroger): Absolutely, I will do that. So the issue is with children who have no spleen. In studies in which pneumococcal congugate or PCV13 and Menactra brand MCV4-D were administered simultaneously there was reduction in the immunogenicity for three of the pneumococcal strains.

And so children with asplenia are at risk from meningococcal disease and pneumococcal disease so we want to optimize the efficacy of the pneumococcal vaccine, which was demonstrated to be reduced when the vaccines were given simultaneously or at short intervals. And so what our recommendations apply to asplenic children and is that the two vaccines should be separated by four weeks and because of the epidemiology of the diseases, pneumococcal infection is a greater risk than meningococcal

infection. This is invasive disease for both. The infection risk is higher with pneumococcas and so we do recommend completing the series of PCV13 and then the interval of four weeks from the last dose to the first dose of MCV4-D. So that's the rationale and the recommendation.

(xxxxx): Thank you very much.

Dr. (Andrew Kroger): You're welcome.

Coordinator: I am showing no further question.

Dr. (Raymond Strikas): Okay, let me - we've got a couple questions that came into us by email. We'll do one at a time and see if more questions appear. Dr. (Kroger), if someone is receiving immunotherapy or treatment for seasonal allergies. Is this a reason to withhold vaccines?

Dr. (Andrew Kroger): Excellent question. No, this is an example of an invalid contraindication. So it is not a reason to withhold vaccines. Allergy shots are specific to these offending allergen for which they're given and do not pose a problem with the effectiveness of a vaccine given later. Someone - note that someone receiving allergy shots is doing something preventive and is usually currently healthy as well.

So, again, the healthy person there's no reason to withhold a dose of a vaccine. If someone were - due or behind for their allergy shots and they had an acute-moderate or severe symptom of an allergy attack, of course, a provider can delay a vaccine in that case, but that's not really what we're talking about here. We're talking about someone going in to receive preventive immunotherapy and so, no, it's not a reason to withhold vaccines.

Dr. (Strikas): Okay, thank you very much. Operator, are there folks waiting to ask questions?

Coordinator: (XXXX), your line is open.

(XXXX): Thank you. I just have one question regarding the difference in the FDA recommendation and the ACIP recommendation for administering zoster vaccine. You know, there's been a discrepancy here for probably the past two to three years since the age recommendation was changed by the FDA and the labeling on the zoster vaccine products. Can you just address why there continues to be that age discrepancy?

Dr. (Andrew Kroger): Yes, I can address that question. So you're correct - CDC recommends zoster vaccine for adults 60 years of age and older, but the vaccine is licensed for 50 years of age and older by the FDA. And the reason for that is that we are taking a very evidence based approached for this vaccine. We have not been able to demonstrate any evidence for a booster dose of vaccine to give more than one dose and when you look at the burden of disease for zoster vaccine - not zoster per se, but the complications of zoster disease - you look at the burden of zoster disease and that burden begins at 60 years of age. And reducing the burden of this complication is where maximal effectiveness with this vaccine.

So what we're somewhat concerned about is that of a dose of vaccine being given to someone younger than that and the new have no recommendation to give follow up doses of this vaccine and that is the nature of why we haven't recommended the vaccine at 50-59 years of age. Now the vaccine is licensed - so you know, providers do have the backing of the FDA, but that's the reason we've made our recommendation. We have no date to recommend a booster dose of the vaccine for when that risk of complication may begin.

(XXX): Okay, thank you.

Dr. (Andrew Kroger): You're welcome.

Dr. (Raymond Strickus): Operator, do we have more questions?

Coordinator: Yes, (XXXX), your line is open.

(XXXX): Okay, my (unintelligible) if I have a patient that is coming from overseas with no record of any vaccination, you know, and I need to start all the vaccinations. How many vaccinations can I give in a day?

Dr. (Andrew Kroger) Great question. It might take me a little bit of time to think about it. The schedule is such that you can give as many as nine vaccines, which would be all of the vaccines recommended with overlap for recommended ages to a person - that is feasible to do if you have to do that. People can withstand hundreds of thousands of doses of antigen. That's the way we've evolved and so the human body can be subjected to that many vaccine doses.

It's probably not going to be that many in most circumstances because for many vaccine-preventable diseases if someone is old enough they age out of the risk and the doses are no longer recommended. So it's not like you have to give every vaccine that was ever recommended in the lifespan, but you should give the ones for which you don't have documentation of vaccination. There are some exceptions to that, you know, with flu season we'll accept a report from the patient that they received vaccine because, you know, people they have to receive flu vaccine every year and so often times there won't be documentation of flu vaccination so you can take self- report for influenza and

we've traditionally said the same thing about pneumococcal polysaccharide vaccine.

That vaccine used to be administered more frequently than we would recommend and we wanted to minimize that. We've often accepted self-report for that vaccine as well. However, with the other vaccines we do not accept self-report and you should take only documentation as proof and you can give all those vaccines that are needed for that age.

(XXXX): Okay.

Dr. (Raymond Strikas): Operator, we can do one more question if there's one waiting.

Coordinator: Yes, the next question comes from (unintelligible).

Woman: Yes, hi. My question - you can hear me?

Dr. (Andrew Kroger): Yes, I can hear you.

Woman: Yes, I have a patient who is teenager - 17 years. Has history of chicken pox as an infant, but no (unintelligible) positive. Should we vaccinate this child with (unintelligible)? You know, or follow the Hepatitis, you know, similar Hepatitis recommendation as - what do we do?

Dr. (Andrew Kroger): Great question. So it's - really, the basis is on your confidence and the history of the disease. I mean if you need to do what we call a provider verification of that history. How confident you are in that actual diagnosis is important. If, you know, if there were siblings that also had similar illness that suggests that it really was varicella and it spread. If there's historical laboratory data in that case during infancy that would be, of course, helpful as

well. But lacking those things you just have to kind of trust your confidence and if there's any doubt you can give a dose of vaccine even if someone has had a case of Chicken Pox.

The birth in the United States before 1980 - I don't remember if that would be applicable here or not, but if that is another criteria as well as long as someone is not a healthcare provider or immunosuppressed or foreign born it doesn't count. That's based on the epidemiology. So, yes, it's essentially kind of your confidence in that history and if there's any doubt we would recommend giving a dose of the vaccine.

Dr. (Raymond Strikas): Okay, thank you for all the questions. That's all the time we can devote to them now. I will mention before I repeat the CE information. We will have, as we've been doing and continue to do, 10 AM next Thursday on July 30 eastern time an hour long session if need be, but we will start a session on Q and A's on this segment. General recommendations part 2 in vaccine safety and details of that will go up on our website shortly. Let me repeat the CE information. For CE credits you see the website I've mentioned several times. The course number, which is date specific is E as in Edward, C as in Cat, 2064-072215. Please note that date specific extension.

The verification code is EPI-Safety. Epi-Safety. You need that verification code. CE Credit expiration is August 24, 2015 for this program today. For help with the online system, which is very to use, but if you need help there is phone help available 8 AM to 4 PM Eastern time at 1800-41-TRAIN or you can email CE@cdc.gov. You can email immunization questions to us if you did not get to ask them today and cannot participate in the Q and A session next week at NIPINFO@cdc.gov and we'll try to respond to those as quickly as possible. You can also call immunization questions at 1800-CDC-INFO at 8 AM to 8 PM Eastern time Monday through Friday.

Additional resources you can use, you know about the Pink book and the website for the pink book is there. It's available online or you can purchase a hard copy and instruction to do that are at that website - that first website. Our CDC vaccine homepage is CDC.gov/vaccines/default.htm and resources for healthcare providers are listed there under the resources website. And we have a Twitter handle - a twitter account at CDCIZLEARN - L-E-A-R-N. If you wish to tweet us about something you're concerned about.

So that concludes our program. I want to thank Dr. (Andrew Kroger) for the presentation covering many topics in great detail and for answering your questions. Thank you very much and have a great day from Atlanta.

Coordinator: This concludes - this concludes today's conference. Thank you for your attendance. You may disconnect at this time.

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